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Council of Canada**

**Conseil de recherches
médicales du Canada**

Guidelines on Research Involving Human Subjects 1987

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Guidelines on Research Involving Human Subjects

**MEDICAL RESEARCH COUNCIL OF CANADA
20th floor, Jeanne Mance Building
Tunney's Pasture
OTTAWA, ONTARIO, CANADA
K1A 0W9**

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Foreword

The Medical Research Council of Canada (MRC) holds that the highest possible sensitivity and moral standards must be applied to all research. In its continuing concern, the Council in March of 1984 established a Standing Committee on Ethics in Experimentation. Council's first request of this multi-disciplinary group was to review the adequacy and currency of the 1978 MRC Guidelines for the protection of human subjects in research.

A Working Group on Research Involving Human Subjects met between February and September 1985 to prepare a draft document designed to raise and deal with the essential issues which the Standing Committee should consider in its report to the Council. The Standing Committee on Ethics in Experimentation then used this draft as a basis for a discussion document.

In the course of this review by both committees, advice was sought from some who worked with the 1978 Guidelines, as well as from Canadian and foreign experts. Thirty five guests accepted invitations to meet with the Working Group or the Standing Committee. Other granting agencies, as well as many health-related bodies and institutions were consulted. Individual and institutional submissions were invited from across Canada, and approximately 750 written submissions were received, including 500 from outside the research community. Meetings of the Standing Committee were open to the media to encourage public interest and input.

Council circulated this discussion document in November 1986 to approximately 2000 persons, including all who had written to Council on this issue. Approximately 120 letters of comment were received and analysed by the Standing Committee in preparing its final report to MRC.

The Medical Research Council of Canada accepted this report as MRC's Guidelines on Research Involving Human Subjects, and requires all research which it funds to be in compliance with these Guidelines.

November 1987

**Members
of the
Medical
Research
Council
Standing
Committee
on Ethics in
Experimentation**

The Honourable Mr. Justice T. David Marshall, The Supreme Court of the Northwest Territories, Yellowknife, *Chairman of the Committee*

Dr. Bernard Dickens, Professor, Faculty of Law, University of Toronto

Dr. Henry Friesen, Professor and Head, Department of Physiology, University of Manitoba

Dr. David Hawkins, Professor and Chairman, Department of Medicine, Memorial University, St. John's, Newfoundland

Dr. Ian Henderson, Director, Bureau of Human Prescription Drugs, Department of National Health and Welfare, Ottawa

Mme. Mary Lamontagne, Vice President of the Board, Centre hospitalier de l'Université Laval, Québec

Dr. Brenda Milner, Professor, Montreal Neurological Institute and Department of Neurology and Neurosurgery, McGill University

Dr. Jean Rochon, Professeur, Département de médecine sociale et préventive, Faculté de médecine, Université Laval

Mr. Robert Rupert, School of Journalism, Carleton University, Ottawa

Dr. Francis Rolleston, Director, Scientific Evaluation, *Secretary to the Committee*

Ms. Judith Miller, Policy Development and Planning Officer

Dr. Richard Bélec, Public Affairs

**Medical
Research
Council
Staff**

**Members of
MRC Working
Group on
Research with
Human Subjects**

Dr. Bernard Dickens, Professor, Faculty of Law,
University of Toronto, *Chairman of the Working Group*

Mme Jacqueline Blanchet, Nutritionist and Gerontologist,
Université Laval, Québec

Dr. John Dossetor, Department of Medicine, University
of Alberta

The Hon. Mr. Justice T. Marshall, Supreme Court of the
Northwest Territories, Yellowknife

Ms. Marion King, Director, Research Grants Division,
Social Sciences and Humanities Research Council,
Ottawa

Dr. Agnes Klein, Bureau of Human Prescription Drugs,
Health and Welfare Canada, Ottawa

Dr. Jean Rochon, Professeur, Département de médecine
sociale et préventive, Faculté de médecine, Université
Laval

Dr. Sydney Segal, Department of Pediatrics, Vancouver
General Hospital

Ms. Janet Halliwell, Director, Research Grants, Natural
Sciences and Engineering Research Council, *Observer*

Ms. Judith Miller, Policy Development and Planning
Officer, *Secretary to the Working Group*

Dr. Francis Rolleston, Director, Scientific Evaluation

**Medical
Research
Council Staff**



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Introduction

The primary aim of these Guidelines is to define the Medical Research Council's expectations of the research community in any research involving human subjects funded by the MRC. Council's first Guidelines were published in 1978 as *MRC Report No. 6, Ethics in Human Experimentation*. This document has become an integral part of the ethical review process in many institutions in Canada. The 1978 Guidelines are being superseded because of the need periodically to update all ethical statements and to guide the review of new research developments.

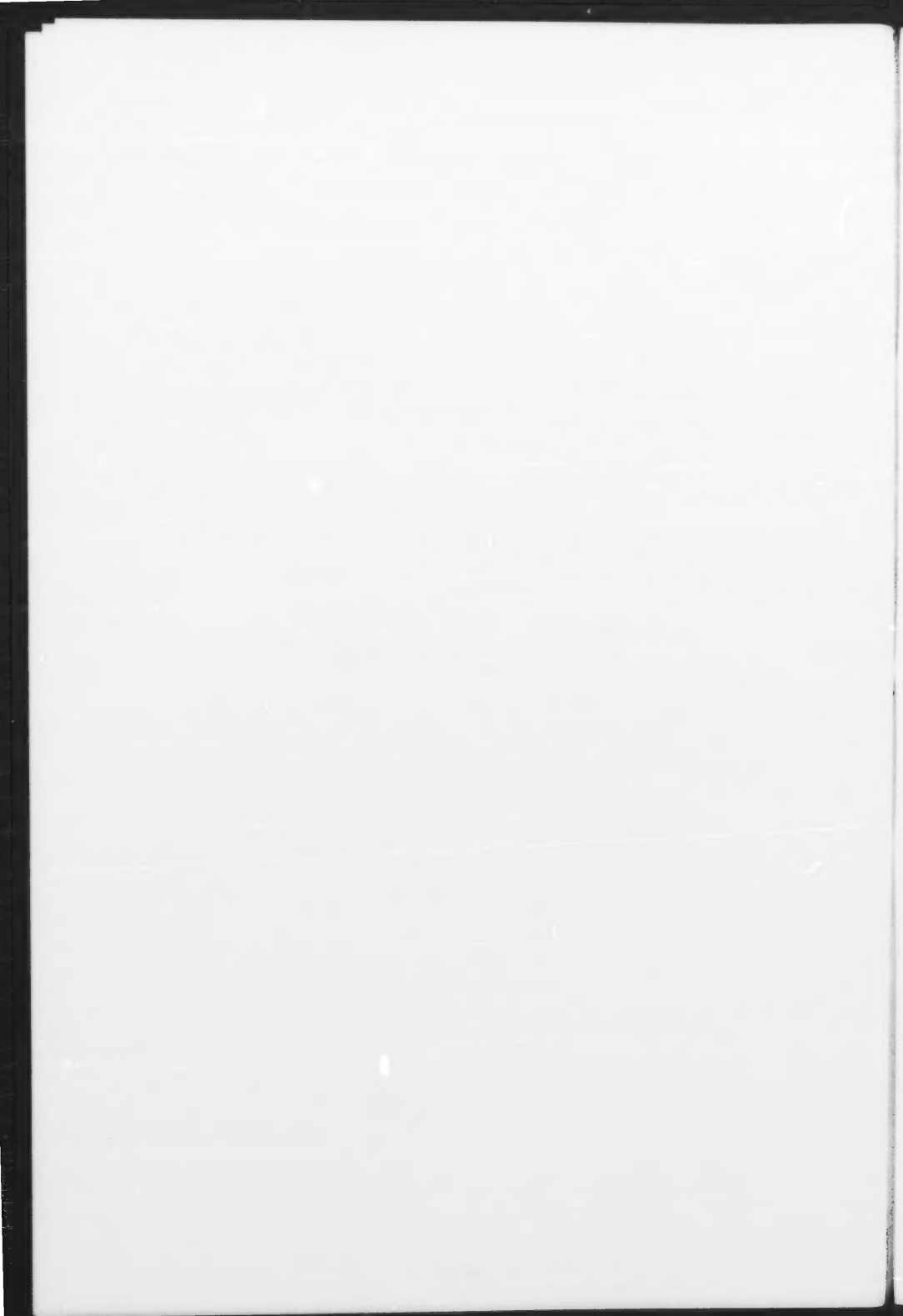
Ethics are principles of right conduct, guiding what ought to be done. Although they may reflect enduring moral values, ethics are not static but evolve with time and public perception. Because the issues at the interface between science and society are so important, the public must be involved. Hence, the audience for the MRC statement of research ethics includes lay members of committees considering the ethics of research proposals and the increasingly interested public beyond. These Guidelines aim as well to stimulate discussion and understanding of human research ethics, and to encourage further development of ethical awareness in both the research community and the broader public.

The purpose of the guidelines therefore, is not to tell those responsible for making the ethical judgements on research proposals what decisions they must reach. Their purpose is rather to sensitize and guide decision makers on the range of perceptions they should bring to bear and to describe the processes of decision making that must be observed.



Part 1

Principles



Chapter I.

Historical Development – Research Ethics

Benevolent paternalism was without doubt a dominant force not only in the early ethics of experimentation but in all social organizations in the early recorded history of mankind. Even the Ptolemies' consent to the vivisection of criminals in the third century B.C.¹ is an example of the ethics of human experimentation at that time. A good measure of this paternalism remained up to modern times. Individual ignorance, poverty and powerlessness would allow the researcher licence limited only by the researcher's power, conscience and religious beliefs of the times. Ethics, it seems, were left to the individual judgment of the physician/investigator.

It is also clear, however, that early experiments with human subjects, undertaken with minimal regulation, have resulted in significant medical advances. These include the discovery by Edward Jenner in 1796 of the preventive vaccination for smallpox through the inoculation of a healthy eight-year old boy. Also, by way of example, major advances were made in yellow fever prevention through the deliberate infection of volunteers with yellow fever in order to confirm disease transmission through mosquito bites (1900). There were, of course, many, many more. On the whole, biological and medical research enjoyed a great deal of freedom, as major experimental advances and improvement of health care reinforced acceptance of this limited ethical guidance.

The philosophy of *laissez faire* in medical research, like its counterpart in the market place, has now been greatly curtailed. This has taken place through the rise of liberalism and western democratic thought. As well, a number of incidents, some of which we will relate, have focussed public interest on medical research and brought about change.

The philosophy of liberalism rests on a number of principles. Foremost among these is the primacy of individuals, their freedom and their right to be left alone. This respect for persons led to the rise of the concept of autonomy.

The origins of this fundamental philosophy, now deeply held in the occidental world, are scattered through ancient, medieval and modern history. A chronicle of Roman Law, the *Institutes of Justinian*, records "Freedom, from which we get the description of men as free, is a

¹ "Public Policy and Human Research," by Albert R. Jonsen, published in *Biomedical Ethics Review*, edited by James M. Humber and Robert Almeder. Humana Press, Clifton, N.J., 1984.

man's natural capacity of *doing what he pleases* unless he is prevented by force or law ..."²

The *Magna Carta* of 1215, Chapter 29, states: "No Freeman shall be taken or imprisoned ... or in any way destroyed ... excepting by the legal judgment of his peers, or by the laws of the land."³

In the *American Declaration of Independence* of 1776, these principles grew stronger: "... endowed by their Creator with certain unalienable rights, that among these are *Life, Liberty and the pursuit of Happiness* ..." ⁴ That Declaration and the British Bill of Rights became the model in France in the Revolution of 1789. The *Declaration of the Rights of Man and the Citizen* followed. It was meant to be of universal application, and states in Article 4, "Liberty consists in the freedom to do everything which *injures no one else*."⁵ The classical statement of this liberal principle is that of Mill: "... the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others. *His own good, either physical or moral, is not a sufficient warrant*. He cannot rightfully be compelled to do or forebear because it will be better for him to do so, because it will make him happier, because, *in the opinions of others, to do so would be wise or even right*."⁶

The elements of consent, so important now in law and ethics, flow in great part from this philosophy.

A number of incidents have focussed public concern on the application of these principles to medical research.

The most shocking was the revelation at Nuremberg of the research atrocities conducted under Hitler on unwilling captives during World War II. This led to the *Nuremberg Code* which emphasized respect for persons and the importance of voluntary informed consent.

² The Institutes of Justinian, Book 1, title III in *The Elements of Roman Law* by R.W. Lee. London, Sweet and Maxwell Ltd., 1956, 4th edition, p. 57. (emphasis added.)

³ *Magna Carta* in *An Historical Essay on the Magna Carta of King John* by Richard Thomson. London, printed for John Mayor and Robert Jennings, 1829, p. 154 (emphasis added).

⁴ The American Declaration of Independence in *The Great Documents of Western Civilization*, by Milton Viorst, Philadelphia, Chilton Books, 1965, p. 166 (emphasis added.)

⁵ *Ibid.*, pp. 189-90.

⁶ John Stuart Mill, "On Liberty", chapter 1, in *Great Books of the Western World*, edited by Robert Maynard Hutchins. Chicago, William Benton, Publisher, 1952, volume 43, p. 271 (emphasis added.)

The need for vigilance in these matters is evident from the fact that there existed in Germany ethical guidelines for experimentation⁷ issued by the German Minister of the Interior in February 1931, well before the atrocities took place.

Abuses were not limited to Germany. Prominent in cases of North American abuse was the so-called "Tuskegee" study. In that case, the US Public Health Service Venereal Disease Division conducted a 40-year project on the effects of *untreated* syphilis in several hundred black men. Initially, no treatment was available, so there was no prejudice to them. But even after the discovery of the effectiveness of penicillin, the study was continued and no treatment was given. This conduct apparently received official approval as late as 1969.

Another celebrated abuse that triggered public sensitivity was a study of cancer through the injection of cancer cells into unsuspecting senile patients in a hospital in Brooklyn, New York.

There have been abuses uncovered in Canada as well. In the case of *Halushka v. The University of Saskatchewan*,⁸ a university student was not told, in the course of his involvement in testing an anaesthetic, either that the drug was new or that a tube would be advanced through his veins to his heart. He claimed grave injury. In that case, Mr. Justice Hall stated:

There can be no exceptions to the ordinary requirements of disclosure in the case of research as there may well be in ordinary medical practice. The researcher does not have to balance the probable effect of lack of treatment against the risk involved in the treatment itself ... The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent.⁹

Though these cases seem outrageous now, ethics are very much related to the times. Jenner's experiments in 1796 undoubtedly passed unquestioned. The same research today could only be conducted on a statistically

⁷ In *Journal of Medical Philosophy*, 1983, volume 8, pp 95-111.

⁸ (1965), 53 Dominion Law Reports (2d) 436.

⁹ *Ibid.*, p. 444. See also *Zimmer v Ringrose* (1978), 89 Dominion Law Reports (3d) 646.

significant sample of consenting subjects in an approved clinical trial.

In the face of an evolution of ethical values and the recognition of cases of abuse, public policy has developed ethical codes to protect subjects of research.

Established subsequent to the Nuremberg Code, the *Helsinki Declaration*, adopted by the World Medical Association in 1964 and significantly modified in 1975, serves as a base for these efforts. In recent years, studies of research ethics have been conducted in France, the United Kingdom, the United States and Canada, among others. In 1982, the World Health Organization and the Council for International Organizations of Medical Sciences elaborated "Proposed International Guidelines" which address special needs encountered in research in developing countries. In Canada, the MRC has built upon the tradition developed in these codes of ethics.

Chapter II.

The Nature of Human Research

A. Research on Human Subjects

Medical research should be a deliberate and careful step into the unknown. Research generally involves uncertainty and it involves risk. These, though confined, can rarely be precisely specified or entirely eliminated.

These standards address research that constitutes scientific health-related interventions conducted with human subjects. In focusing upon research in the health sciences, these Guidelines address scientific study relating to prevention, diagnosis, management and therapy in the health care of individuals and human populations.

For the purposes of this document, research refers to the generation of data about persons, through intervention or otherwise, that goes beyond that necessary for the individual person's immediate well-being. Intervention is not just medically defined, but includes acts which affect a subject's interests in, for instance, physical integrity, intellectual and behavioural integrity, and privacy. Much research with human subjects is physically non-invasive. Sociological studies and consultation of a patient's record, for purposes exceeding the patient's health care, constitute research with a human subject. Health sciences research may involve nothing more than taking a blood sample. But research may also involve more invasive procedures, such as comparative evaluation of surgical interventions. Research accordingly ranges from very sophisticated multi-centre controlled clinical trials, to a retrospective statistical review of a former patient's health record, or the study of the form and function of cells from an identifiable subject under varying conditions.

A "subject" of research may be defined as a human being who directly bears any risks of the research to be carried out. The harms that may be incurred are legion and include not just inflicted injury but also loss of dignity and self-esteem, guilt and remorse, or feelings of exploitation and degradation.

B. The Research Process

Research with human subjects is one element in an evolving process. Prior to proposal of a formal scientific protocol with human subjects, an investigator conceives of an hypothesis to test. Often research is the next logical step beyond theoretical knowledge of existing therapy or other management. An unusual occurrence may on occasion trigger research; for example, Alexander Fleming's astute observation that no bacteria grew around mold on a contaminated culture led to the development of penicillin. The idea may be developed through observation in nature, through experiments in or analysis of cell or tissue cultures, and through use of model systems, animals or other means.

Continued development toward rigorous scientific research with human subjects is likely to involve pilot studies with a limited number of subjects to test initial feasibility. This may be done, for example, to develop and refine investigators' techniques, and to improve the quality of information that prospective subjects of the scientific study can subsequently be given.

Methodologically sound scientific proposals for research with human subjects emerge from such a continuous process. Research itself is but a part of the ongoing process. Discoveries from research may then be utilized in health care and health promotion. Finally, retrospective research to evaluate prior work may ensue.

C. Methodology and Ethics

Modern scientific research must conform to the requirements of rigorous methodologies. Thus, scientific research has its own integrity. It is accepted that ethical research must be scientifically sound, so that observing the integrity of the scientific method is part of the ethics of research.

However, scientific integrity may also present more general ethical dilemmas. The risks of research, for instance, should be applied to the smallest possible population and not involve unnecessary subjects. At the same time, a smaller than required number should not be proposed, because the exposure to risk is unlikely to achieve a scientifically valid result.

D. Therapy and Research

The interaction of therapy and research must be carefully considered. Although separate domains, often the two overlap in human experimentation and perhaps here, more than anywhere else, is the integrity of the physician-researcher tested. The area of conflict is this: in the practice of medicine, the physician's duty is to the patient. The physician makes a diagnosis, and, if the patient agrees, measures of therapy in the best interest of the patient are then undertaken. Decisions taken must respect the patient's interest first. In the Committee's view, it is axiomatic that the treating physician's duty to act in the best interest of the ill patient must never be compromised. In contrast, in research the investigator has identified a research question and conceived a research protocol to attempt to answer it. The commitment here is to answer the research question.

An informed patient may consent to enter a research study but, if therapy is also involved, the best interest of the individual must be the highest concern of the physician responsible for care. *The patient is always entitled to the best clinical judgment of the physician, and research considerations must never displace this.* This is true even if the patient requires innovative treatment that, while therapeutically appropriate, is also of research interest. Since the innovation is intended for the patient's therapeutic benefit, the treatment is not research even though the results may be of wide interest and benefit.

We believe that no one should interfere with the therapeutic freedom of the treating physician. The physician alone, with consent, bears the awesome responsibility of piloting the patient through the shoals of illness. The physician's uncompromised attention should be on the best interest of the patient. But medical advances can and often do emerge from innovative therapy. Even though the identifiable data may be more anecdotal than systematic, their use will be in fact research. Accordingly, research ethics are applicable, not only to the treatment itself, but to use of the resulting data.

The resolution of the therapy/research question rests on the integrity of the physician/researcher. The wide powers afforded in therapy leave physicians answerable to themselves and ultimately to professional peers and, through the courts, to the patient and the public, for irresponsible and negligent conduct. Research, on the other hand, is conducted, planned and directed toward new knowledge. It is to research then that the considerations in these Guidelines apply.

E. Guidelines or Legislation?

Decisions in medical ethics depend on striking a balance between competing ethical claims. Many decisions in society depend on such balances. The law, expressed either through the political process which creates legislation, or through judicial determination which creates governing precedents, undertakes the task of resolving many of these competing interests. Legal rules form a foundation, and the law is a minimum ethic.

The question arises: Should the MRC propose legislation rather than guidelines to regulate research with human subjects? In that way, the rules provided would carry the usual sanctions of law and thereby might have more force.

The Standing Committee does not consider legislation to offer an appropriate response to all the ethical dilemmas which arise in research with human subjects, for a number of reasons. The least of these is the difficulty of achieving nationwide standards under Canadian constitutional provisions. The *Criminal Code* is a federal statute, but research proposals affecting such matters as health, hospitals, universities, majority age and mental competency fall within provincial jurisdiction. The *Criminal Code* already applies to medical research, for instance in its provisions on assault, but its control can be heavy-handed, and its enforcement usually requires proof of wrongful intention established beyond reasonable doubt. Provincial legislation, for instance on tissue donations and release of medical data, is also relevant to research, but its enforcement has many of the unsuitabilities of the *Criminal Code*. It may be more sensitive in that it can accommodate the fine tuning of regulations, but it presents the possibility of lack of national uniformity in its provisions.

Legislation and regulation under law prescribe standard responses to anticipated scenarios. Its potential to apply justly consists in its treatment of broadly-defined categories of like cases in like ways, and in the finding of operative facts by the authoritative due process of the courts. The ethical assessment of a research proposal may raise a wide range of interests and values, some novel, and may require risk-to-benefit determinations which cannot easily be prescribed or standardized. The facts of ethical priority cannot always be authoritatively established; particular factors may weigh differently at different times and in different circumstances. A proposal may be rejected as premature at one time and be acceptable only a short time later, for instance, because of evolution in the field of inquiry in question.

Research under Guidelines is not immune from legal scrutiny, and is not conducted in a legal vacuum. Surrounding law, both federal and provincial legislation (or territorial ordinances) and the general law declared by the courts, is applicable and has to be observed. The Standing Committee believes, however, that at this time the use of Guidelines within the current body of law is sufficient to reinforce the ethical conduct of research with human subjects. Guidelines can accommodate more easily than law the shifting social evaluations that affect research, and can influence responses in subtle ways rather than with the rigidity often found in legislation. Further, guidelines can exert an influence beyond their strict limits, while legislation tends to mark the limits of its influence.

Guidelines can be abused; their successful operation requires trust, local commitment, and administrative structures in both local and central locations to interpret them with good will. The Standing Committee believes that Guidelines, administered responsibly in an atmosphere of public openness and within a society that respects the judgments of its different parts, can be an effective instrument of ethical control. Indeed, the truly ethical quality of the assessments to be made may atrophy when judgments are directed by law.

F. Law and Ethical Responsibility

The relationship between law and ethics is the subject of extended philosophical debate, but an initial proposition is that an ethical obligation exists to act in accordance with legal requirements.

While breach of the law is generally unethical, a mere conformity with it may not be sufficient for discharge of responsibility. Whether an individual acts or not will often be governed by ethical rather than legal principles.

Although the law often compels obedience to behavioural norms, ethics aim to inculcate an awareness of values which may develop with practice and which may have to accommodate choice and liability to err. The practice of obedience to law does not necessarily develop awareness of ethical values. This development may require resolution of dilemmas and exercise of judgment rooted in subjective perceptions.

G. The Fundamental Principles

It is an aim of these Guidelines to promote the development of ethical awareness in investigators, Research Ethics Boards (REBs)¹⁰ and the wider community. The discharge of ethical responsibility at all levels of involvement may require the consideration of options and the exercise of choice. These Guidelines propose criteria and procedures for the exercise of such choice.

The *Canadian Charter of Rights and Freedoms*, enacted since the 1978 Guidelines, is a new and powerful legal force in Canada. Ultimately, the higher courts will have to rule on the law in regard to such matters, and present speculation may well prove unsound. Legal advice should be available to investigators and REBs, whether from members of the REB, from the institutional solicitors or indeed from outside sources and should be considered, when necessary, to take account of the Charter. The Charter governs relationships between individuals and public agencies. Complaints of Charter violations may come from anyone whose rights under the Charter have been infringed.

The Standing Committee believes that the basic ethical principle in research, as in health care, is respect for life. From this principle flow others: the concept of autonomy, the duty to beneficence, and the duty to justice.

Respect for life both justifies and limits research. As for beneficence, mankind may benefit, but individuals place themselves at risk. The benefits and risks of research must always be weighed. Justice must be exercised in allocating the anticipated risks and the hoped-for benefits.

The burden of the enterprise should run with the benefit. Great care must be taken that research risk does not fall unjustly on the infirm, or the racially, economically or otherwise disadvantaged.

The assessment of risk and benefit calls for a most careful study of the relevant data. Both the investigator and the institutional REB must assess the risk to benefit ratio, bearing in mind that risks and benefits may accrue to different people and not be measurable on the same scale.

¹⁰ "Research Ethics Board (REB)." This name is chosen for the institutional board reviewing medical research proposals, to indicate its emphasis on the ethics of research, in contrast to the previous MRC (Canada) use of "Ethics Review Committee," and the US title, "Institutional Review Board."

The ratio must be clearly favourable before the proposal can gain ethical approval.

Upon institutional approval of the study, the subjects' participation may be invited, and they too must be able to make their own assessment of the balance between likely benefits and risks to themselves and others, and perhaps to those for whose welfare they are responsible.

The ethical challenge then is to decide in the light of principle what risks are justifiable and for whom, in relation to presumed gain. These dilemmas are the central focus of the Guidelines.



Chapter III.

The Evaluation of Risk and Benefit

**How Scientifically
Valid is the
Research Proposal
and what are the
Potential Benefits
from the Research?**

**Should this
Research be done
at this time?**

**Is the Group of
Research Subjects
Appropriate?**

Research should be undertaken only if the potential benefits outweigh the potential risks. Difficult decisions must be made. Their range can be indicated by posing a series of questions.

Since the potential for knowledge depends on the scientific merit of the research, evaluation of scientific merit is essential to ethics review.

Because an REB cannot be scientifically competent in all the areas it must address, some have argued for separate review of science and ethics. The Committee does not agree with this view. Since ethics review demands a balancing of risks and benefits, the ability to determine whether a research protocol is scientifically valid, taking whatever external advice may be necessary, is essential if an REB is to carry out its functions.

Although the accumulation of knowledge about the human mind and body ultimately requires research on human subjects, much can be learned from prior research. The use of human beings in the research must be essential for scientific reasons and should be based on data from appropriate preliminary research on animal or other models, wherever possible. The research should not repeat work already done unless such work requires further substantiation.

The significance of the results sought, in terms of improved therapy or better understanding of physiological or psychological phenomena, must be considered in the context of the research subjects. The potential benefits of research should carry greater weight if the anticipated results can be applied directly to the treatment of the subjects themselves.

It is for this reason that the balances between risks and benefits must take account of the group in society from which the subjects are to be drawn. Ethically, the strongest justification arises when the research hypothesis directly concerns members of that particular group, who thus both bear the risks and may enjoy the benefits.

What are the Identifiable and Potential Risks?

The investigator and the REB must determine, as completely as possible, both the known and the potential risks involved in the research regimen. Consideration must be given primarily to the risk of physical or psychological harm to the subjects. Attention should also be paid to the degree of harm that the subjects, as a group, may suffer, as well as to any potential or foreseeable harm to society as a whole if the research is allowed to proceed. Such a determination is required not only to evaluate the risks of the research, but also to provide potential subjects with sufficient information on which to base their informed consent.

Is the Research as a Whole Ethically Acceptable?

The foregoing questions illustrate the complexity of evaluating a research project. Balancing the various issues raised depends on perceptions of standards that may vary from community to community and that may evolve with time. It is for this reason that REB members should be drawn from as wide a sample of the regional society as possible.

The flexibility needed to allow the exercise of ethical judgment for each protocol may impair apparent consistency in the review process. Different REBs may balance ethical dilemmas of identical protocols differently, and the same REB may consider the same issue differently at different times. The urge for consistency should guide but not govern the review process.

Chapter IV.

Special Types of Research

A. Genetic Engineering

Some research raises special concerns, perhaps because of the methodology, the purpose, or the subject matter.

New capabilities in genetic manipulation make consideration of ethical issues in this area a particular concern.

Some fear that genetic engineering may bring about a fundamental change in the very nature of human beings. The most likely and practical applications of genetic engineering in human beings, however, closely resemble well-accepted medical interventions and provide promising approaches to correct certain well-understood, but currently untreatable, genetic deficiency diseases caused by a single defective or missing protein.

Current technology allows isolation of individual genes, their transfer into body cells, such as bone marrow cells, and return of these modified cells with functioning new genes into the organism. Another technique, as yet at an early stage of testing, is germ-line genetic engineering. This changes not only the genetic character of the individual but of the offspring as well, because it affects sperm and ova, the germ cells. The ethical implications in this type of transfer cause grave concern. There are profound difficulties in estimating risk and benefit.

In the present state of knowledge, the Committee advocates consideration of human genetic engineering only where there is no reason to believe that the genetic alterations will be inherited, and only when long-term follow-up is an element of the research proposal.

B. Pilot Studies

Pilot studies are undertaken, for example, to test innovative therapy, to explore an idea, to determine whether the logistics of a proposed research protocol will function, or to train people in a new technique. Pilot studies are valuable to guide more detailed investigations, but do not, of themselves, answer scientific questions, unless the results are unexpectedly definite. Nonetheless, they are research and require ethics review if they involve human subjects.

The REB, in considering a pilot study, must assess potential benefit in a different perspective from that for a full study. The benefit of a pilot study is the guidance it gives on the design or implementation of a full study. The study may show that the logistics of the design need modification, that the new treatment has unexpected side effects, or that the methods of measuring the outcome of

the intervention do not work as expected. Well-designed pilot studies provide essential guidance using far fewer subjects than a full study. The REB must ensure that the reasons for the pilot study are well defined, and that the design, including the number of subjects, will produce reliable data. The REB should also be confident that, if the pilot study succeeds, a full study will follow.

C. Clinical Trials

Clinical trials may demand a number of techniques: these include randomization, blinding and being multicentred. Subjects are said to be randomized in a study when the choice of the intervention they receive is determined not by the patient or the clinician but by an independently generated list of randomly ordered allocations to the test or control intervention. Subjects suitable for inclusion in such research are to be assigned randomly to the two treatment groups so as to avoid, as far as possible, any conscious or unconscious weighing of the patients selected toward one or the other intervention. This is a standard technique used in the assessment of the relative efficacy and safety of alternate treatments. Randomization does not differ from other models of research, in that general ethical principles apply. Particular care must be taken, however, in such studies with patients, to ensure that the subject's best interest is never sacrificed to that of the randomized study.

In addition to being randomized, a study may be blinded. As a result, in comparing two treatments or interventions, neither the subjects nor those treating the subjects, know until the end of the study who received each treatment. The purpose of this, like randomization, is to minimize bias, in this case in the ascertainment and assessment of study outcomes.

A randomized clinical trial, or indeed any other experiment, may be undertaken in a single centre, or a study may be arranged in a number of centres, that is, it may be a "multicentre trial." Multicentre trials raise unique ethical and practical concerns. Pressures on an REB to comply with decisions taken in other centres cannot be accepted. Because parallel concerns may be raised in different institutions, it is important that REBs which are considering the participation of their institutions in a multicentre trial communicate with each other about the concerns raised in their discussions. If necessary, joint meetings of representatives of the different REBs should be convened. Also, the REB in one centre may ask that certain changes be made in the protocol for it to proceed within its own institution. If these changes are such as to prevent valid pooling of the

resulting data with the data from the other centres, then that institution should not enter the collaborative multicentre trial. This problem may be limited by communication and liaison between REBs themselves or through the MRC. Through communication, one REB might be persuaded to vary its ruling for the sake of the study program, but no pressure should be applied or permitted which reduces institutional autonomy or compromises its sense of propriety.

D. Drug and Product Testing

Studies on drugs or products, whether sponsored by manufacturers, the MRC or other institutions, when they involve human subjects, require approval by the REB at the institution involved.

In these cases, it may be necessary for the REB to interact closely with Health and Welfare Canada, and the protocol should clearly state whether Health and Welfare clearance is necessary for the testing. In requesting this clearance, a company is required to submit extensive details and data on the product under investigation. These data are submitted under guarantees of strict confidentiality due to their commercial nature.

The extent to which universities and hospitals permit their personnel and facilities to undertake private research, not intended for scholarly publication of results, is for each to decide.

Commercially-directed research may raise questions of concern by its very nature. Inducements to research personnel or subjects and the ultimate ends of the research should all be considered.

The professional integrity of the principal investigator, the vigilance of the REB, and a critical consideration of all the ethical, medical and scientific aspects of using human subjects for commercial rather than truly scientific purposes will, we believe, lead to proper conclusions should questions arise.

E. Transplantation and Device Implantation

Research in these areas is often considered to be innovative therapy rather than research. However, in clinical trials in these areas, the Guidelines will apply.

The allocation in society of scarce organs or costly devices and procedures raises ethical issues of growing and grave concern. However, this Committee views these issues as relating more to therapy than to research, and hence does not address them in these Guidelines.

F. Social Science Studies in Health Care

Some health care research with human subjects may follow the scientific methods of the social sciences. As the vision of health-related considerations has expanded, psychological, sociological, and economic dimensions of individual and community health have become apparent. Accordingly, much research is conducted consistently with the methods and values of the social sciences. For this reason, investigators of all disciplinary backgrounds who present proposals for social science studies in medicine should conform to both the MRC Guidelines and the consistent Guidelines on research ethics of the Social Sciences and Humanities Research Council of Canada.

Chapter V.

Principles of Consent

A. Informed Decision-Making

The law of consent has been much debated and has recently undergone a good degree of development. The law is technical, and a measure of forensic precision is required in addressing this aspect of the Guidelines.

The cardinal principle of research on human subjects is that, to the extent that it is possible, a subject's involvement should be informed and voluntary. Ideally, subjects should be fully informed, and should make their decision on whether to participate at leisure and in complete freedom from any pressure. Practically speaking, this is rarely, if ever, possible.

Potential research subjects seldom have the knowledge needed to evaluate fully the scientific information on which the research is based. Much research involves people who are under care, and thus feel themselves under pressure to participate. Some potential subjects may be mentally incapable of the discussions or comprehension needed for consent, through reasons of mental illness, trauma or age. Decisions may have to be taken too rapidly to allow transfer of information or reflection on information, because delays might be against the therapeutic interests of the patient. However, research is necessary if the care of people in these situations is to improve.

The obtaining of informed consent is only one step in a continuing process. The educative effort commences before and continues after the signing of a document, and continuing consent must be elicited during the progress of the research.

Put simply, prospective subjects must receive, in a language which they understand, enough information about the proposed study and their prospective role, to enable them to decide whether or not to participate. Investigators must anticipate what information may be important. They can be guided by tailoring the disclosure to a reasonable person in the circumstances of the prospective subject.

The research protocol must outline what information is to be given to prospective subjects. Copies of information sheets should be submitted to the REB as well.

A protocol will normally be expected to state what prospective subjects will be told; these points may include:

- a) the reasons for the study;
- b) research techniques which will involve the prospective subject, such as randomization of treatments;
- c) the reason why the prospective subject is being invited to take part;
- d) the reasonably anticipated benefits and consequences of the study itself;
- e) the reasonably anticipated benefits and consequences of the study for the prospective subject and society (if none, this should be stated);
- f) the foreseeable risks, including discomforts and inconveniences, to the prospective subject;
- g) the foreseeable risks of the study itself;
- h) complete details regarding confidentiality of prospective subjects;
- i) the anticipated time commitment for subjects;
- j) the intent to conduct a follow-up study in the future and the retention of data;
- k) the rules for stopping the study and withdrawing the subject; and
- l) the right of the subject to withdraw from the study at any time and without penalty.

Additional information requirements must be met for potential subjects who are also patients and whose care may be directly affected by participation in the study. Information would include:

- a) the patient's prognosis without intervention;
- b) alternative interventions available;
- c) experimental aspects of interventions proposed;
- d) interventions to be unavailable to a patient who becomes a subject, for the sake of the research;
- e) an estimate of the likely success and failure of all the interventions which may be offered and withheld;
- f) an estimate of the risks and possible adverse effects of interventions offered; and

- g) a clear distinction between procedures in the research protocol and those that would be part of usual patient care.

The level of disclosure should be proportionate to the likelihood and the scale of possible harm, but even the remote possibility of injury should be disclosed.

B. Free Consent

The invitation to a prospective research subject must be made in a way that allows the individual freedom of choice. Sufficient time to reflect is important. It need scarcely be said that undue influence must not be employed. Prospective subjects, for example patients who are asked by those responsible for their care to serve as subjects, may feel pressure which investigators do not at first perceive.

The law recognizes unequal relationships as inherently suspect. In such relationships, the law presumes that any agreement between a weaker and stronger party, from which the stronger party gains unusual advantage, is tainted. There is little doubt that such a relationship exists when patients are asked by those treating them to serve as their research subjects.

In such cases, physician-investigators must do their utmost to ensure and maintain their patient's independence. The invitation to participate in a research project must always be proffered in a manner that fully describes the objectives of the study, and outlines the reasons underlying the selection of suitable patient participants. In general, the clinician who is to be responsible for the research study is in the best scientific position to implement this early phase of subject enrollment. Notwithstanding the fact that patients almost invariably bear a sense of dependency on their personal physicians, often coupled with a sense of allegiance and at times with a degree of anxiety about their future health care, care must be taken to avoid coercion or undue influence, both of which can reduce independently arrived at consent.

Communication of the final decision, to participate or decline, may be difficult for the patient if the question is posed directly by the physician who will be responsible for continuing care. Under these circumstances, it may well be desirable to delegate the ultimate decision-seeking question to another member of the health care team, possibly another health professional who has no direct link to the patient's future medical management.

A single consent and information form provides a useful permanent record of the essential information given, and records consent. The subject must be given a copy of this document, which should also provide other information, such as a name and telephone number to allow the subject to ask questions about the project later, and to remind the subject that he or she can decline to participate or withdraw from the project at any time without any prejudice to future rights. The subject must receive information about remuneration, if any. If the investigator or institution is not insured, the subject must be informed.

Evidence of consent is almost invariably obtained in writing. In the province of Quebec, this is legally required (see art. 20, *Civil Code*). Outside Quebec, consent may occasionally be allowed to be taken orally, but, whether in written or oral form, there should generally be an independent witness to the consent. In very minor cases, consent may be implied by the subject's freely entering into the research project; a subject voluntarily completing an anonymous questionnaire would be an example.

C. Induced Consent and Payment

Improperly induced consent like pressured consent is unacceptable. Particular populations, such as students, laboratory staff and technicians, to name but a few, may consider it advantageous to volunteer for participation in a study.

Such groups are readily identified and often accessible. It may be convenient to use them when knowledge applicable to the general population is sought. As a result, certain groups may be asked repeatedly to serve as research subjects. While they may be happy to participate, there are reasons in justice to distribute the risks as well as the benefits of the research more widely throughout society.

Beyond the advantage of career progress or security is the inducement of money or the offer of free medical or dental care for subjects or members of their families. Such inducements must be treated as rewards and be assessed under the same principles. Remuneration limited to compensation for expenses actually incurred and losses reasonably assessed, including loss of wages, is ethically acceptable, provided that it does not distort freedom of choice but facilitates collaboration by indemnifying subjects for their direct and indirect expenditures. Payments for time and inconvenience, if nominal, are similarly acceptable. Excessive remuneration, or other advantages or benefits, however, are an improper

inducement to participate in a research project. The REB must have information about remuneration and determine whether it is reasonable.

D. Continuing Consent

Consent to participate in research as a human subject arises in a collaborative relationship between investigators and subjects; it is not a contractually-binding commitment. Subjects are informed that, even though their consent is in writing, they may leave the study at any time without prejudice to their rights, and they must be free to do so. Research must not become dependent upon the continued participation of any particular subject in order to maintain the statistical validity of data. Subjects should not be offered such rewards for participation as will constrict their freedom to leave a study. Reimbursement should therefore be as expenses are incurred.

Prospective subjects must be informed of the duration of their involvement in a study. This includes the duration of any procedures involving them, such as physical or psychological testing, and also the duration of retention of identifiable data. If such identifiable records are to be kept, prospective subjects have a right to know that their consent to involvement in the study includes continuing consent to retention of data.

E. Non-Consensual Research

Epidemiological research has greatly advanced medical science and should be fostered.

Research on identifiable human subjects, without their prior informed and free consent, has been seen to be contrary to principle, but it may be ethically permissible in limited circumstances. Research upon subjects incapable of consenting is considered in a following section. Other research may be ethically conducted, however, to which the competent human subjects do not consent. In cases such as epidemiological research where records of patients may be reviewed, the potential benefit and the degree of compromise of the patient's confidentiality must be carefully weighed by the REB. In these studies, often human subjects' medical conditions are reviewed, but identifiable individual cases may not be. Confidentiality must not be unduly compromised. If identifiable data are used in epidemiological research, and prior consent is not to be sought, the prospective investigators bear the responsibility of showing in the protocol that it is ethical for the requirement of consent to be waived, and that adequate means exist to ensure the confidentiality of the data.

This holds even if the records concern people who are now dead. The essential issue is the possibility of harm from indignity felt by the patients or their relatives resulting from use or release of information.

If a study involves the public conduct of subjects, their consent may be waived if the conduct is purely spontaneous and not conditioned or influenced by any act of the investigator and the subjects are neither identified nor identifiable. The behavior will be available to an investigator's scrutiny by reason of its being voluntarily undertaken in public, even though subjects do not expect the purposeful and systematic scrutiny of their acts. Even where confidentiality is not at stake, care must always be taken to protect subjects' identities, and they must be treated with dignity and respect.

Consent is generally unnecessary for research undertaken, for example, upon surplus blood, urine, tissue, and similar samples obtained for diagnostic or treatment purposes if the patient is not identifiable, and the requirements of the research do not influence the procedures used for obtaining the samples.

F. Deception

The MRC is committed to both openness and accountability. In view of the critical importance of informed and free consent, consideration of deception seems incongruous.

Although deception is not used in the vast majority of medical research, the Standing Committee was advised that some areas of behavioural or psychological research can only be carried out if the research subject is not aware of the reasons for the research.

Deception involves the intentional misleading of prospective subjects or withholding information from them, so that subjects believe that the procedures or the objectives of the research are different from what they actually are. Deception may include deliberate presentation of false information, suppression of material information, or selection of revealed truths in a way designed to mislead.¹¹

¹¹ Placebos. The use of placebos which amounts to deception should be distinguished from the situation where the subject knows that an inactive substance may be used and agrees to its possible use. Placebos are defined as medicines given to humour rather than cure (*Concise Oxford Dictionary*, 7th ed., 1982).

Because the concept of deliberately misleading research subjects runs so much counter to the principle of respect for the individual, the Committee had great difficulty accepting that deception could ever be ethically justified. However, should research situations arise where it is essential to scientific integrity that the subjects remain unaware of the nature of the research, the following rules should be applied. Such situations warrant particular scrutiny by the REB.

1) Deception should not be used where any other methodology would accomplish the research objective. The investigator should demonstrate in the protocol that no other method is feasible.

2) Research involving deception should not be carried out where there is any reasonably anticipated risk to subjects; it is impossible to justify exposing subjects to risk when they have not consented to incur that risk.

3) The REB should be satisfied that nothing is withheld from the subjects which might, if divulged, cause them to refuse to participate.

4) The REB should be satisfied that significant scientific advance can be expected from the research, in order to justify even minimal deception.

5) Deception should be permitted only when it is possible to inform and "debrief" subjects afterwards and to obtain subsequent consent to use the data obtained. Debriefing procedures should be written into the research protocol and should take place immediately following participation in the research, while the data remain identifiable. It must be recognized that debriefing does not remedy deception. Data obtained from subjects who subsequently decline to participate should be destroyed or surrendered to the subjects. This in itself, we think, will discourage the use of deception.

G. Consent with Special Populations

G.1. Cross-cultural Studies

Issues in research with distinctive ethnic or cultural groups require discussion, since research proposed to the MRC includes some to be conducted in different cultures. Apart from its inherent medical aspects, such research may raise issues more familiar to those in the social than in the medical sciences. The other cultures are not necessarily in other countries; studies with Canada's indigenous peoples or other culturally distinct groups may concern cultures different from those of the investigators.

In other cultures, individual consent may have a role which differs from its usual role in broad Canadian society. In most of Canada, it expresses personal autonomy, reinforced by law, the Canadian Charter of Rights and Freedoms, and ethical perceptions. Societies

under a tribal or inherited leadership may not prize individualism to the same extent. They may consider it subversive of communal order, or may believe the first duty is to community not self, and even consider excessive devotion to liberal principles and respect for the individual the height of selfishness and hence immoral. Proposals for research may be considered first by tribal leaders and elders rather than by individual potential subjects. If tribal leaders approve the proposed study, it does not follow that one may apply procedures to individuals without their own consent. A leader's approval may be a necessary but not a sufficient condition for undertaking study of individual subjects. Concepts of privacy and confidentiality may also differ among cultures. Such concepts must always be viewed from the perspective of the culture studied, as well as from that of the investigator.

In meeting these needs, an investigator involved in cross cultural studies should be expected to meet all of the requirements normally expected in ethical review, as well as the additional requirements necessitated by the use of the distinct cultural group.

G.2. Research Involving Legally Incompetent Subjects

By definition, a legally incompetent subject is not autonomous, and cannot give a legally or ethically valid consent. However, these people may suffer illnesses on which research is necessary if methods of therapy are to be improved or instigated. In some cases, the illness may cause the incompetence. Some of the needed research may be expected to benefit the research subjects, but other needed research may not.

Research involving incompetent subjects therefore may raise conflicts on legal and ethical grounds. Strictly interpreted, the law of assault and the principles of common law preserving autonomy and requiring consent may be seen as proscribing subjecting these people to risks of harm not undertaken in their immediate interest. The great problem for society is that any hope of progress in prevention, diagnosis and treatment of these very processes that give rise to the incompetence require research on these same people.

The Standing Committee is acutely aware of the great problem that this dilemma raises on both sides. The discussion which follows concerning research on the children mentally incompetent and attempts to give some guidance to investigators and to REBs in this most difficult area.

G.2.a. Research Involving Children

The ethical challenge is to determine the conditions and limits under which children may be involved in medical research. How far may parents or legal guardians go in committing their children to be the subjects of necessary research?

A relevant measure is that society and parents should not expose children to greater risks, for the sake of pure medical research, than the children take in their everyday lives. Parents control this level of exposure now.

Parents may consent to inspection of their children's medical records for research, and may similarly approve collection and analysis of collected excreted materials, provided that the method of collection causes no pain or, for an older child, embarrassment. They may permit others to handle their children in ways that would otherwise constitute a technical and minor legal assault, but not where pain or discomfort beyond carefully defined limits would be liable to occur.

The conditions under which children can volunteer for non-therapeutic interventions of no benefit to them are contentious;¹² much centres upon the level of development of the individual child and the surrounding circumstances. A child's agreement may be mere toleration without comprehending, or it may come close to informed consent as conventionally understood. Chronically ill children may gain a better understanding of medical procedures than would be expected of other children in the community.

A concept has developed that a child incapable of giving legally and ethically acceptable consent may give an "assent" which is significant in respecting a level of autonomy. Related to this concept is the recognition that a child, whose consent or assent to participate in research is questionable, may nevertheless have the power to decline invasive involvement with conclusive effect. Parental consent may be a necessary condition of engaging the child in research, but it is not necessarily a sufficient condition; the child's negative preferences in such cases should be respected.

Regarding older children and adolescents, it may be appropriate to initiate discussions with them, and, if they appear to favour participation, to say that their parents' approval will be necessary. A mature adolescent willing to

¹² Their existence is denied by some authorities. See *MRC Report #6*, 1978, p. 30. See also *Re Eve* *1986, 2 S.C.R. Page 327. (SCC)

**G.2.b. Research
Involving Mentally-
Incompetent Adults**

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participate in a study has a claim to respect for privacy and to freedom of participation, under vigilance of an REB.

The child's physician or family physicians may give parents valuable advice in that they may have no commitment to particular research proposals or institutions, and therefore nothing to conflict with concern for the children's welfare. Further, the child's physician must be aware of any interventions in children's routine care, for discharge of their ongoing responsibilities; they may be approached by investigators, even before parents, for guidance on the medical propriety of the child's participation.

The legal capacity of children to consent must be adjusted, of course, to relevant provincial legislation or regulation on the age of consent to medical treatment and, when this gives no guidance, to the maturity of the individual child.

Mentally handicapped individuals cannot be presumed to be incompetent to comprehend information and exercise choice. The issues must be determined on the facts of each case. Where intellectually-impaired adults are assessed to establish their mental capacity, the principles outlined above regarding children and adolescents may be applicable in principle. Important differences may exist, in that such adults may not be under clear legal guardianship and, at one time in their lives, may have achieved adult status, competence and personality. Accordingly, their treatment must reflect their mature personalities and, in particular, avoid any procedure which the subjects would probably have refused, were they still fully competent. The ability of all incompetent potential subjects to exercise choice must be maximized, and their dignity must not be compromised by exposing them to procedures which demean them or exacerbate their dependency.

Particular caution must be exercised when incompetent adults have been under institutional care for some time, because family members may not be as sensitive to their personalities and preferences as would be those with whom they live. Senior officers of the institutions where they reside may also be unable to consent, because they are not the legal guardians (unless properly appointed); they have an administrative responsibility for such adults rather than a relationship based upon personal affinity and allegiance. Institutional heads should nevertheless be consulted, because they may have clinical or pragmatic

objections to their patients' taking part. When patients' moods are being therapeutically conditioned, care must be taken to ensure that research is not proposed in circumstances creating likelihood of favourable responses.

Research into disorders of the elderly pose special problems. Research into Alzheimer's disease, for instance, may require affected subjects to be exposed to uncomfortable and above-minimum-risk procedures. Subjects may not themselves benefit from results of individual studies, and they may lack competence to give consent. Their guardians, whether *de jure* guardians properly appointed, or *de facto* guardians such as family members, may not have legal power to give effective consent to invasive procedures. Indeed, mentally and physically-disabled persons' legal protections are strengthened under the *Canadian Charter of Rights and Freedoms*, reducing the likelihood that provincial public hospital, mental-health or mental incompetency legislation would be construed to allow such research not related to therapy. Rights to integrity of the mentally-disabled protected by law and the Charter cannot be reduced or compromised simply upon the basis of decisions of REBs; only courts have authority to approve invasive forms of management, and to say what consent process will be adequate for invasive non-therapeutic procedures. The points that we have outlined in regards to the limits of the use of children in research will apply equally here.

Mentally-incompetent adults with whom research may legally be conducted present special problems as well when they are institutionalized. As such, they are similar to patients, prisoners, or, for example, members of military forces. Their will may be conditioned by their surroundings and by the influence of personnel having control of their comforts and environments. They may also be induced by the promise of advantages to which those in free circumstances would not respond.

Where non-invasive procedures, such as medical record review, are involved, appropriate discussions should be initiated with potential subjects with a view to obtaining at least their assent, if they are at all capable of consent. Further, projects may be discussed with accessible community groups concerned with the mentally-disabled, such as mental-health associations. Such groups cannot give consent, of course, but exposing proposals to their review may satisfy the REB that due consideration has been applied to a proposal. Such associations may be invited to review other proposals, such as studies involving risk of discomfort, limited deprivations or, for

G.3. Research with Fetuses and Embryos

G.3.a. Research on Fetuses

instance, randomization. A member may be invited to advise or join the REB.

At this time, the legal status of embryos and fetuses is not well defined, nor is the social consensus. While issues of consent and autonomy may not therefore apply, clear ethical concerns arise from the unarguable fact that embryos and fetuses are human life forms.

A research program directed to an expectant mother cannot avoid consideration of the fetus. Studies directed at the fetus may concern prenatal diagnosis, or *in utero* methods of treating the fetus. Those directed toward the pregnant or potentially pregnant woman may include trials of drugs which might be used by pregnant women, for reasons unrelated to their pregnancies. Studies aimed at the process of reproduction may include both mother and fetus. Since the mother and fetus are inextricably linked, the REB must consider fully the risks and benefits of the protocol on both.

Separated tissue and placental material may be regarded as routine pathological tissue, and may be used in research, subject to the permission of the mother whenever possible and to provincial human-tissue-gift legislation and hospital regulations.

The issue of legal abortion has an obvious impact on proposals for research upon pregnant women, fetuses and fetal tissues. Where a woman is to have an abortion induced before her fetus is capable of independent survival, it may seem that the additional risk to the fetus posed by research is not a factor. The decision to abort, however, can be changed until the abortion procedure itself is irreversible, and only then can the possibility be discounted that the mother may change her mind. In research designed to be performed under such conditions, the research protocol must not influence the procedures used for the abortion, nor affect the viability of a fetus, nor prejudice the welfare of a child upon birth.

A fetus living at birth, even if it is not viable, is treated under the *Criminal Code* as a human being, whether or not it has breathed, has an independent circulation, or the umbilical cord is severed (s. 206(1)). Causing injury before birth, as a result of which death occurs after birth in a living state, can constitute homicide (s. 206(2)). Accordingly, living fetuses, and fetuses liable to be born living, must be treated under principles applicable to children. Nothing can be done to impair viability, nor to

risk the health of such a newborn child, except perhaps when a favourable risk-to-benefit ratio is clearly established in research designed to improve the life chances of the immature newborn.

G.3.b. Research on Embryos

The human embryo is no less a unique human life form than a fetus and warrants a high order of respect. Some believe no embryo research whatsoever should be allowed, no matter what the foreseen benefits of such research and foreseen risks of not conducting such research. Other believe that embryo research is of critical importance in understanding and correcting problems in human infertility and development, and believe research with embryos, in principle, to be no less appropriate than research with other human life forms. Research to reduce neonatal death and birth defects in children, for example, may benefit from embryo studies.

The recent emergence of *in vitro* fertilization as a treatment for infertility has caused embryos to be created in the laboratory, and thus has raised the possibility of embryo research. To increase the likelihood of pregnancy, it is sometimes the case that more embryos are created than are needed to be implanted in the patient, and more embryos are implanted than are expected or intended to develop. This loss of embryos mirrors the high rate of loss which occurs in natural reproduction, as well as in artificial insemination. The possibility of research with embryos which remain after *in vitro* fertilization, or with embryos available from other sources, poses contentious issues on which there is no social consensus. Difficult questions arise as to whether any research with embryos should occur, and if so, until what state of gestational development and under what conditions; whether research should involve unused embryos only; or whether embryos may be created especially for research.

Many groups have addressed these difficult questions. The issue of the stage of gestational development, if any, up to which research may be allowed, has achieved quite consistent responses internationally from reasoning proceeding from different premises. The recommended limit of about 14 days can be shown to lack a philosophical basis and not to provide a point of significant biological discontinuity in embryonic development. It may accord, however, with a pragmatic sense of ethical acceptability, and it coincides with the legal distinction between contraception and abortion which turns upon implantation of the embryo in the uterus of the mother. The overwhelming preponderance of legal opinion holds that abortion provisions apply after

implantation, and that techniques to prevent conception or implantation of a conceived embryo constitute contraception.

However, this legal position does not answer the ethical issue of whether research even up to 14 days' gestational development is acceptable. Despite the legal distinction between contraception and abortion, some oppose such a means of contraception and, consistently with this, would also oppose this extent of embryo research.

A further problem with a 14-day limitation is that, if natural implantation failure and loss or spontaneous abortion are to be reduced, the mechanism of implantation itself must be studied. To limit embryo research to the point of implantation would accordingly prevent study of the process and its failure. Extension of this time limit may permit conduct of research which will reduce the rates of natural wastage and spontaneous abortion.

Restraints on embryo research have reduced the clinical research phase which properly should precede or accompany adoption of new techniques in clinical practice. It may be viewed as unethical not to conduct supportive research designed to assess and improve the safety and efficacy of such procedures as *in vitro* fertilization and embryo freezing. Without such research, therapeutic advances become limited and haphazard.

The Committee views embryo research as an evolving area where Canada does not have a social consensus and where individual values are strongly held, but also evolving. Although there is an opportunity for abuse in the use of *in vitro* fertilization in embryo research, as in the application of any technology, the Committee sees a broad prohibition of all research on embryos as neither justified nor wise. Decisions on the details of research proposals involving embryos will vary with regional and individual differences, and thus the local REB is an appropriate forum in which to assess each protocol. In reaching its decision, an REB must take into account the embryo as human life at an early stage of the life cycle and the purpose for which the research is proposed. Wherever reasonably possible, such research should be undertaken instead with non-human life forms, or with tissues from abortuses.

At this time, the Committee believes that the purpose of intended research is a critical element in deciding whether embryo research is acceptable. In the Committee's view, it

is not acceptable at this point to create embryos *in vitro* for research as opposed to therapeutic purposes. The Committee believes that for now such research should be limited to research directed toward improvement of infertility management, using embryos up to a stage of development of no more than 14 to 17 days. Research designed to establish the safety and effectiveness of procedures such as *in vitro* fertilization may especially merit consideration. In time, with the evolution of social and ethical values and further scientific development, REBs and investigators might contemplate other embryo research for such purposes, for example, as genetic correction.



Chapter VI.

Confidentiality

As in therapy, the general rule in research is that confidentiality cannot be breached without the subject's consent. The rule is a strict one, and should be observed from the beginning of the research initiative. The ordinary ethical requirement of confidentiality is reinforced by two principles of research: a) patients should not be approached by strangers who know their medical circumstances, and b) the management of patients should not be influenced by their decision not to participate.

Where subjects give consent to research, access to personally identifying information and its use in research must be guarded. Identifiable data should be coded at the earliest possible time and involve a minimum number of research staff. No one outside the research team should be permitted to handle identifying data. Only those who need to link the data to a particular subject should be able to do so. Junior staff in the research program should be impressed with the need to guard data against disclosure through discussion in the company of persons outside the program. Identifiable data should be held secure from theft, copying, interception and casual release.

Publication of research findings cannot allow for subject identification without prior consent. If identifying information is to be maintained for the purpose of contacting subjects for later projects, or for long-term follow-up of effects of treatment, this intention must also be disclosed to the subject.

A particular problem of confidentiality arises in investigations of the genetic or familial aspects of disease. Investigators may want to approach a subject's relatives to gather additional data or to warn of potential implications. Access to relatives must in principle be controlled by subjects themselves; subjects may be anxious to protect the confidentiality of their medical conditions particularly from their families. No approach for research purposes can therefore be made without a subject's consent. Consent may be more easily given when confidentiality of the subject can be maintained, but that may not be possible in genetic studies. Even when subjects consent, approaches to family members should be through them rather than directly through investigators, because individuals must not be approached by strangers bearing intimate information about them. Alternatively, physicians of family members may be asked to act as intermediaries.

An investigator's wish or sense of duty to warn family members against genetically-based risks of severe harm, for example, from certain activities or foods, may be controlled by general rather than research ethics, but the issue should be considered by the REB. A legal duty to warn of the circumstances may override obligations of confidentiality.

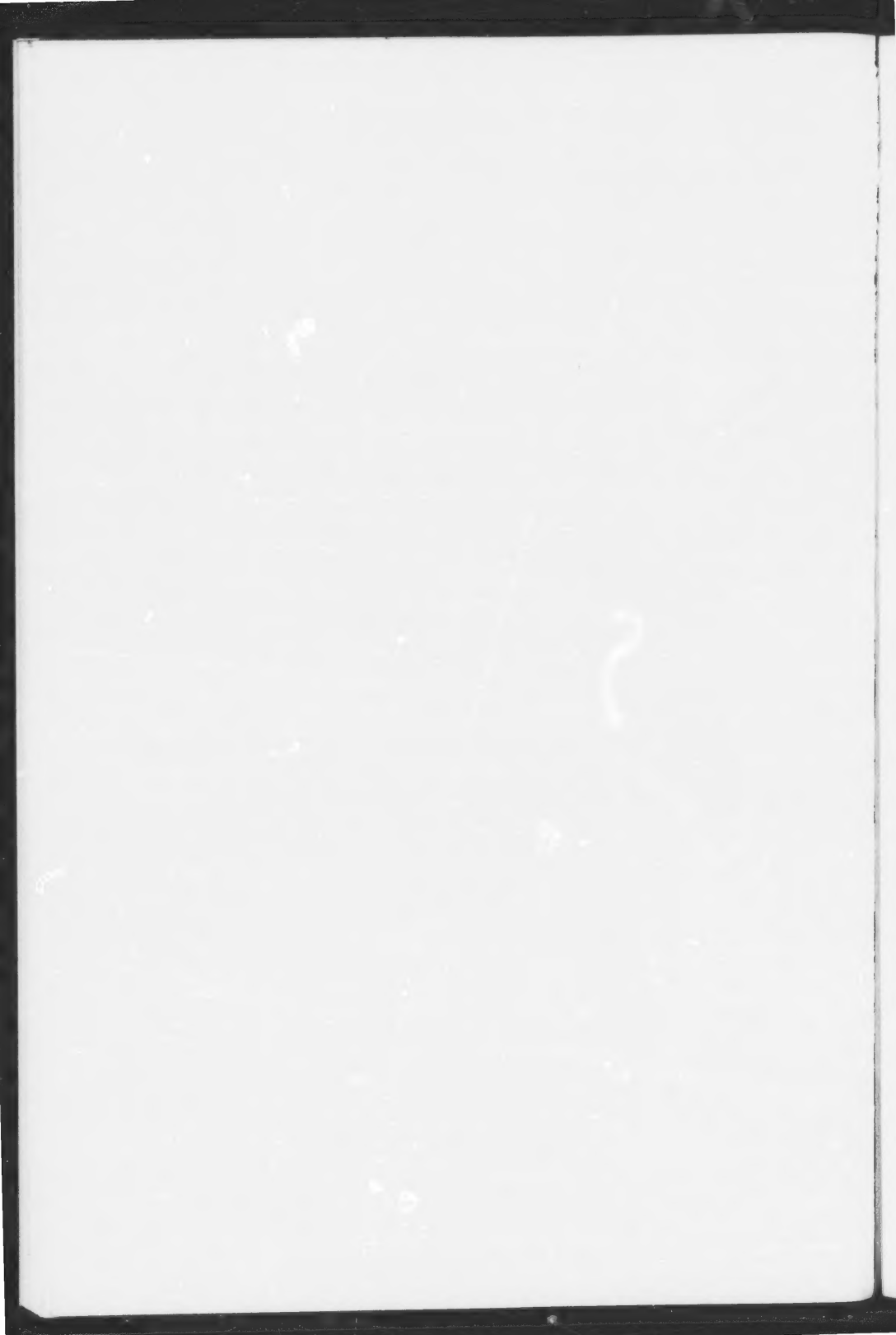
When potential subjects are offered undertakings of confidentiality, care must be taken not to promise more than can be achieved. Apart from legal duties to warn mentioned above, research records are liable to subpoena. Courts and judicial tribunals always have final power to require disclosure either in a restricted or public way.

Accordingly, potential subjects may be only offered protection of confidentiality within the limits of the law. Destruction of data not subject to a restraining order of a court may protect confidentiality, but at the cost of not being able to contact subjects upon later evidence of risk to them, or of follow-up studies, of re-calculation of data, or of investigators' means to explain and defend their methods and their findings.

Part 2

Practice

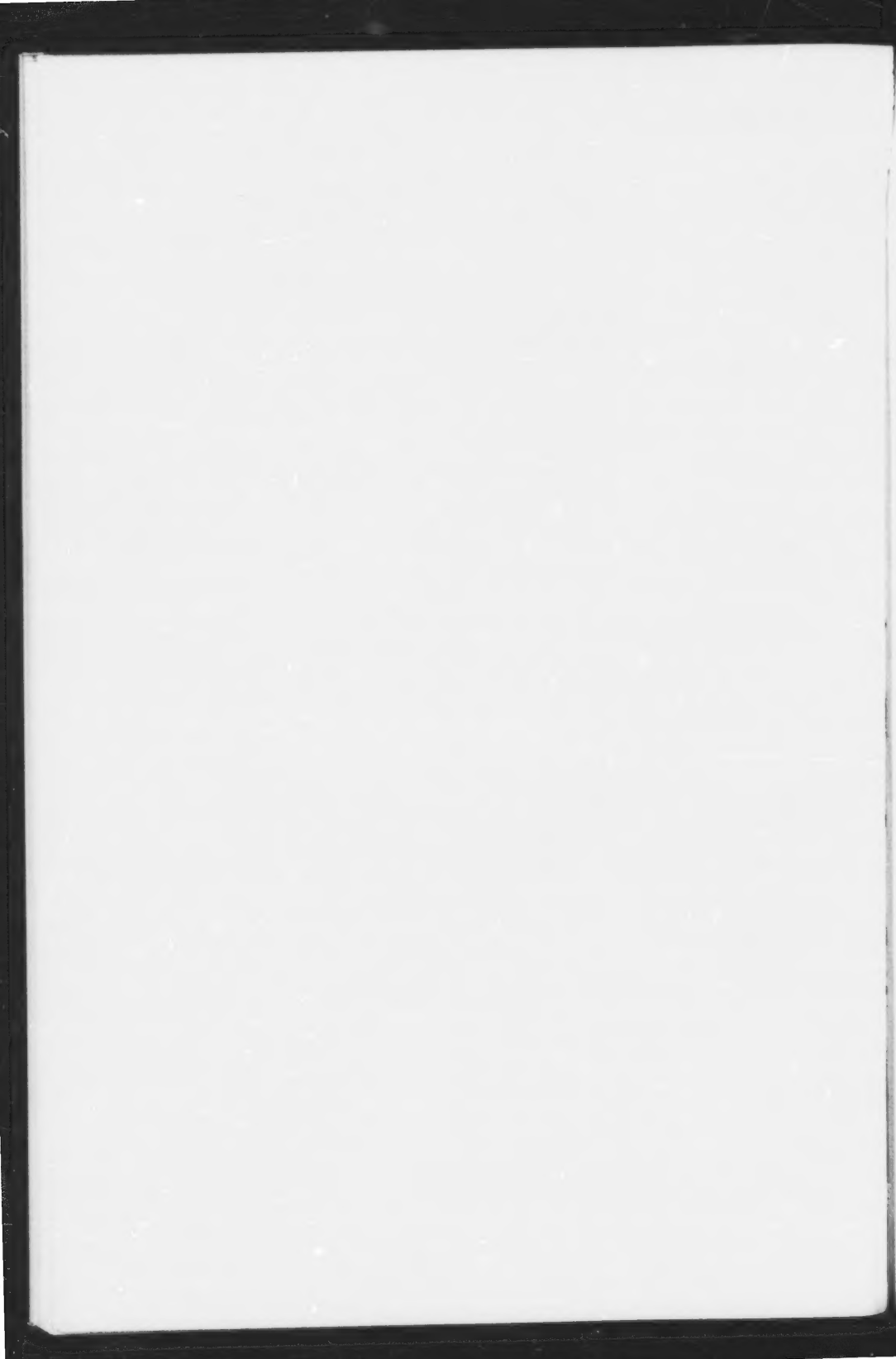
Implementing Ethical Responsibilities



Introduction

The MRC Standing Committee on Ethics in Experimentation, as well as the Working Group, examined requirements for ethical review in a number of institutions across Canada. This included procedures and practices for the assessment and surveillance of human experimentation. The Committee also considered ethical control in other jurisdictions. As a result of the Committee's research and deliberations, and consideration of the submissions of the public and the research community at meetings over a two-year period, the procedures recommended to Council are more stringent than those in the 1978 Guidelines.

Responsibility for the proper conduct of human experimentation lies with all who are involved in the research, but most particularly with the researcher and the local REB. The MRC must ensure that public funds are spent only on research that is ethically acceptable.



Chapter VII.

Responsibilities

A. The Researcher

Researchers have the initial and continuing duty to ensure the ethical conduct of all aspects of their research. The researcher must identify and bring to the attention of the Research Ethics Board (REB) any factors which might raise concerns, both as part of the process of obtaining approval from the REB, and also as the research proceeds. It follows that, in every case, the researcher responsible must be clearly identified and unequivocally take on responsibility for the proper conduct of the entire research team.

B. The Institution

The institution within which the researcher works has the major responsibility to ensure that the research meets the ethical standards of society. Although researchers apply to MRC for grants, the funds are administered through the institution, which acts as trustee. The terms of the trust include not only management of accounts, but also active responsibility for initial and ongoing conformity to proper standards. The Committee reaffirms the role of REBs in undertaking the institution's responsibility for the ethics of research undertaken with MRC support.

C. The Medical Research Council

The MRC has assumed responsibility for providing guidance in research involving human subjects and for ensuring that its funds are used only within acceptable standards. This is achieved through guidelines and by fostering awareness of ethical issues relating to research involving human subjects. The Committee is of the opinion that in discharging its public trust, the MRC must monitor local procedures and practices in ethics review.



Chapter VIII.

Procedures

A. The Institution

The primary responsibility for decisions on the ethics of research, carried out within the institution or by its staff, should continue to be delegated to Research Ethics Boards (REBs). The Committee has concluded that the REB should be established under the authority of the President or Principal of a university, or a comparable chief executive officer of a non-university institution. This person must give the REB a clear mandate for review of all protocols for research involving human subjects. Also, the REB's relationship to other committees concerned with ethical matters, for example, to professional, teaching or other related bodies, must be defined. The President, Principal, or their equivalents, should give the REB full authority for ethics review.

The REB should be a standing body which meets regularly. Its membership must be defined, and it should turn over periodically so as to blend experience with fresh perceptions. In addition, the workload of each REB should be sufficient to assure an experienced Board, but not so large that attention to necessary detail suffers. Therefore, in large institutions, more than one REB linked through some central system may be formed. A multiplicity of small local REBs should be avoided.

A.1. Composition of the Research Ethics Board

The Standing Committee is cognizant of the fact that there is wide variation in the organization and composition of REBs. The Standing Committee believes, however, that the Guidelines should outline minimal expectations for an REB, such as we describe here. This proposed composition is intended to be illustrative.

The Community

The values of the particular community are the matrix of ethical review. The REB must contain members who can reflect community values. Lay members affiliated with a hospital or university board are often suitable, but the board should ideally include non-affiliated individuals. Community bodies may assist in the selection of such members.

Relevant Specialists

The REB should contain at least one specialist in the relevant discipline of the research. The specialist may be a permanent member of the REB or an *ad hoc* member.

A clinical psychologist or other mental-health expert may also aid in assessing the subject's capacity to understand the protocol and exercise a free choice.

Scientists with a broad understanding of research design and of research in the areas usually considered by the REB should sit on the board.

Nurses should be represented on an REB which deals with clinical research.

Other disciplines

Bioethicists, philosophers or theologians will also contribute greatly to the work of an REB.

Since common law and legislation often impinge directly on the decisions an REB will need to take, the Committee regards the presence of a lawyer as desirable. The lawyer should not sit to represent the institution, but to provide legal expertise.

The Committee recognizes that REB members undertake a major responsibility on behalf of the public, and that considerable demands are made upon their time. Service for two to three years, and a high rate of attendance at meetings, are necessary to develop and use the needed expertise.

A.2. Submission of Projects for REB Review

Evaluation by an REB of a research protocol is the major step through which the community can be certain that its values are respected. A document addressing the ethical aspects of a specific research protocol may be very different from one seeking research funds, particularly when the grant application sets out a program of research lasting for a number of years. Therefore, it should not be assumed that the research grant application is always suitable for ethics review, and the REB should require a document tailored to its needs.

The Standing Committee notes with approval the efforts which have been made in some institutions to provide guidance through specific questions or checklists on the material needed for review, and encourages Council to establish broad standards across the country. The materials submitted should include at least the following considerations:

The scientific validity of the proposed research

The documents submitted to the REB should provide, for the specific experiments proposed, sufficient scientific information about such factors as the current state of knowledge, the research design and the methodology, to enable the REB to satisfy itself that the proposed research is scientifically valid.

The appropriateness of performing the experiments on human subjects

Applicable information derived from previous experiments with animals or with human subjects should be described and the need for the proposed experiments on human subjects should be justified.

The risks to subjects of the proposed research

All procedures that could possibly cause harm to the subject must be fully and precisely described. Any known risks arising from these procedures should be made clear, and potential risks should also be assessed as far as possible. Possible alternative protocols should be discussed in order to demonstrate that the one selected minimizes risks. Procedures for preservation of confidentiality must be specified, as must the precautions taken to ensure medical surveillance when subjects are to be placed under stress.

Potential research subjects

The persons to be approached as potential research subjects should be described. This requirement has special significance for research that is not directed to a specific disease and in which the investigator may wish to approach, for reasons of convenience, groups like prisoners, students, employees, or others, in whom free choice is compromised.

Care should be taken that the group of potential research subjects is not already being overtaxed by other research projects.

Procedures for informed choice

Procedures for approaching potential subjects for the research should be described in detail. The description should identify persons who will seek their approval and any others who will be present during the obtaining of consent.

The document should also include a statement of the criteria to be used in selecting the individuals from a general group. The description should also include details of the information to be given to the potential subjects, including any written material to be used in connection, for example, with surveys to be conducted by mail. Where proxy consent is to be obtained on behalf of those unable to consent for themselves, the procedures to be used and the proxies to be approached must be specified.

The consent form must be provided as part of the research protocol. This form should contain statements of the aims of the project, of the procedures the subject will undergo, and of the risks inherent in those procedures. The form should also contain statements of other relevant factors, including side effects of proposed drugs or treatments, which a reasonable person might be expected to consider before giving consent. The form should describe the areas of uncertainty in the research, including the statement that the procedures are experimental and that the subject may not benefit from the research. There should also be a statement that the subject may withdraw from the project at any time for whatever reason, and with no prejudice.

A.3. Accountability of the Investigator to the Research Ethics Board

The approval of an REB for a specific protocol is based on the exact and detailed information available to it. The REB may require changes to the protocol as a condition of acceptance. The investigator is then bound to act in accord with the statements made in the submission as approved. If changes are desired in any detail that pertains to the subjects of the experiment, the investigator should seek the further approval of the REB prior to implementing them. The investigator should also immediately report to the REB any apparent risks beyond those predicted and, if necessary, suspend the experiment pending clarification.

A.4. The Operation of the Research Ethics Board

Certain procedures are necessary if an REB is to meet its responsibilities to the institution and to the MRC.

The Standing Committee is certain that regularly-scheduled meetings are needed for the REB to discharge its duties, and that prior circulation of agenda material, with sufficient time to prepare for the meeting, is essential. The REB may allow its chairman to make interim decisions between meetings in certain areas, subject to ratification by the full board. Some committees may delegate some decisions to the chair, with the

protocol circulated for discussion at the initiative of members.

The Standing Committee recommends that the REB establish, with the President, Principal, or other equivalent institution head to whom it reports, requirements for attendance at meetings, a quorum, and the majority needed for approval of a project. The chairman should conduct the meeting so that all points of view are fully addressed by the REB.

The REB chairman or secretary may identify projects needing external appraisals by scientists or others, and arrange for the reviews to be done. Their reports should form part of the documentation submitted in advance to the REB.

An REB need not be supported by an extensive secretariat, but it is important that minutes be kept. These should capture the issues raised and the assessments made, as well as the undertakings given and facts asserted as relevant to the study. The assurances by researchers to the REB may be critical to the assessment that the proposal can be ethically conducted. Since crucial points and undertakings may not be expressed elsewhere, the documentation of the terms and understandings upon which approval was given should include the minutes of the REB. Further, a record of the REB deliberations is valuable for circulation to interested parties, such as other REBs in the same institution or in other centres in a multi-centre trial, government agencies responsible for licencing a drug, or the MRC.

A.5. Continuing Review

The Standing Committee believes that the REB and MRC should ensure that the actual implementation and conduct of the project continue to meet the standards of ethics agreed to among the researcher, REB, and the MRC.

As part of its initial discussion on ethics, the REB should determine whether audit or review is necessary in each case. If so, the procedures should be set by the REB as one of the conditions of approval. If no ethics audit or review is deemed necessary, the reasons should be given. The plan may provide for inspection of the means by which information is given to prospective subjects, or for an independent assessment of how much those thus informed understand what they have been told.

At a minimum, researchers should be required to provide an annual update on the status of any project for which the REB has given approval. This information should

indicate any changes that may have occurred in scientific knowledge or in the design of the study, as well as the progress of the study. For specific protocols, the REB should also be able to require more frequent or rigorous review.

Once REB approval has been given, the researcher must immediately inform the REB of any new information that might alter the ethical basis for continuing the research program.

It is expected, however, that the institution's monitoring will be more active than simply seeking investigators' assurances. Research officers, or members cognizant of ethical concerns, may be required to maintain scrutiny by periodic review of the research and of the factors involved in the ethics approval. The actual form of this monitoring will vary with the specific research protocols. In certain cases, specialists from outside the institution might be asked to act as monitors.

Investigators' applications to REBs should be countersigned by heads of departments or others with senior administrative responsibility. Notification of ethics approval, including minutes of REB meetings and amendments to the original protocols, should be relayed to such officers, thus placing them on notice of commitments made and accepted. Their institutional obligations in the management of their departments and personnel will help ensure compliance with these conditions.

The costs of this monitoring may transcend financial aspects, to include time taken from the monitor's other activities. Monitoring may also strain professional and personal relationships between colleagues or provide increased opportunities for a breach in confidentiality of information about research subjects and premature release of scientific or commercial information.

The Committee believes that researchers and institutions should bear the costs of this day-to-day monitoring, which are largely similar to monitoring practices already well accepted in the health professions and commercially-sponsored research. The human costs of monitoring can often be reduced through mutual understanding of ethical duty and public interest. Monitors must be impressed with their own ethical responsibilities in accepting the task, and department heads must recognize their institutional duties to arrange adequate monitoring. Investigators must recognize that monitoring is intended

to assist them in meeting commitments they have made in the cause of good science and good ethics.

Finally, it must be stated that the Standing Committee does not believe that appropriate attitudes in research can be ensured by these intensified procedures of monitoring alone. A high standard of ethics results not from policing but from human awareness and personal integrity.

B. The Medical Research Council

B.1. Review of Applications

Applications to MRC for research funds are reviewed by Grants Review Committees which report to Council. Scientists are asked to judge the scientific merit of the research proposed, the funding required and the duration of support.

Review of the ethics of the research proposal is also an essential part of the grants review process. However, the opportunity for review is limited. The applications, which are written primarily to address scientific issues, and which are limited in length, cannot fully address specific questions of ethics, and therefore are not ideally suited to ethics review. Also, many applications request long-term funding and cover many individual prospective experiments.

The Standing Committee believes that the grants review process should continue to review, to the extent that it is able, the ethics of the grant application, as well as the science. Also, the MRC should transfer back to the researchers and the REB any comments by the Grants Committee on the ethical aspects of the application, whether or not MRC funds the research, as this information may be of value to the REB and the applicant.

B.2. MRC Support of REBs

In support of the ethics review process, the Committee recommends that the MRC encourage ongoing information exchange and education concerning issues in the ethics of research with human subjects. One mechanism envisaged is the support of workshops intended especially for REB members and researchers. Another mechanism is regular communication between MRC and members of REBs and others interested in the ethics of research. This communication could provide a steady flow of information and would also afford the opportunity for the REB to learn how others are handling similar problems. Such educational means are necessary to deal with issues not explicitly covered in the Guidelines, either because of the degree of specificity or because of new developments in research.

The Standing Committee is certain that the Medical Research Council must establish mechanisms, perhaps with other agencies, to ensure the effective functioning of the local REBs on which it depends for review of the ethical aspects of research involving human subjects. While these Guidelines place the primary responsibility on the REBs, the Standing Committee is strongly of the opinion that public accountability demands that MRC monitor the functioning of the REBs which review the work that it funds.

**A Selected
Bibliography of Codes
and Guidelines for
Protection of Research
Subjects**



1. International Codes

The Nuremberg Code. Reprinted in *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, vol. 12: 81-82. Washington, DC: US Government Printing Office, 1949. Also printed in Medical Research Council of Canada. *Ethics in Human Experimentation*, pp. 59-60, 1978.

World Health Organization and the Council for International Organizations of Medical Sciences. *Proposed International Guidelines for Biomedical Research Involving Human Subjects*. Geneva: Council for International Organizations of Medical Sciences, 1982.

World Medical Association. "Declaration of Helsinki" (1964). *World Medical Journal* 19(2): 29, Mar.-Apr. 1972. Revised 1975. *Ibid.* 29(6): 86-88, Nov.-Dec. 1982. Also printed in Medical Research Council of Canada. *Ethics in Human Experimentation*, pp. 61-64, 1978.

_____. "Guidelines for Medical Doctors concerning Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment in Relation to Detention or Imprisonment." Declaration of Tokyo. September 1975. *World Medical Journal* 22(6): 87, 90, Nov.-Dec. 1975.

2. National Guidelines

Australia

National Health and Medical Research Council. "Report by NH and MRC Working Party on Ethics in Medical Research". Canberra, Australia: National Health and Medical Research Council, August 1982.

Canada

The Canada Council. "Ethics." Report of the Consultative Group on Ethics. Ottawa, February 1977. (Available from the Social Sciences and Humanities Research Council, Ottawa K1P 6G4)

Canadian Nurses Association. "Ethical Guidelines for Nursing Research Involving Human Subjects". Ottawa: CNA, April 1983.

Canadian Psychological Association. "A Canadian Code of Ethics for Psychologists," Ottawa: March 1986. (Available from CPA, Vincent Road, Old Chelsea, Québec J0X 2N0)

Health Protection Branch and Pharmaceutical Manufacturers' Association of Canada Medical R&D Section Liaison Committee. "Guidelines for the Conduct

of Clinical Investigation." Ottawa: Health Protection Branch, Health and Welfare Canada, December 1985.

Social Sciences and Humanities Research Council of Canada. "Ethics Guidelines - Research with Human Subjects," Annex H in *Research Grants Guide for Applicants*. Ottawa: July 1986. (Formerly "Ethical Guidelines for the Institutional Review Committees for Research with Human Subjects." Ottawa: September 1981.)

France

Information concerning the following documents can be obtained from the:

Centre de Documentation et d'Information d'éthique
des Sciences de la Vie et de la Santé
101, rue de Tolbiac
75654 Paris Cedex 13
France

Comité consultatif national d'éthique. «Problèmes d'éthique posés par les Essais chez l'Homme, Nouveaux Traitements, Réflexions et Propositions.» France: 9 October 1984.

«Droits de l'Homme, Pratiques Biomédicales et Comités d'éthique à travers le Monde.» Milieux, no volume (23-24): not paginated, 1986. (Institut Dumay, Le Creusot.)

Lettre d'Information du Comité Consultatif National d'éthique pour les Sciences de la Vie et de la Santé, July 1985 to present.

Ministère de la Justice, «Éthique et Droit en Amérique du Nord Face au Développement des Sciences Biologiques et Médicales, Rapport de Mission (4 septembre - 5 octobre 1985),» prepared by Christian Byk, Magistrat, Direction des Affaires Civiles et du Sceau, 1986.

«Éthique et Droit en Amérique du Nord Face au Développement des Sciences Biologiques et Médicales, Documents Annexés au Rapport de Mission (4 septembre - 5 octobre 1985),» prepared by Christian Byk, Magistrat, Direction des Affaires Civiles et du Sceau, 1986.

United Kingdom

Warnock, Mary, Chairman. "Report of the Committee of Inquiry into Human Fertilization and Embryology." London: Her Majesty's Stationery Office, July 1984. (Cmnd 9314)

"Responsibility in Investigations on Human Subjects." [Annual] Report of the Medical Research Council for 1962-3 (Cmnd 2382), pp. 21-25. Reprinted in British Medical Journal 2: 178-81, 18 July 1964.

"Responsibility in the Use of Medical Information for Research." Annual Report of the Medical Research Council for 1972-3, pp. 10-16. Reprinted in British Medical Journal 1: 213-16, 27 January 1973.

"Ethics of Investigations with Human Subjects: A Set of Principles Proposed by the Scientific Affairs Board." Bulletin of the British Psychological Society 30: 25-26, 1977.

United States

National Commission

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles for the Protection of Human Subjects of Research*. Washington, DC: US Government Printing Office, 1978. Dept. of Health, Education and Welfare (now Health and Human Services), publication # (OS) 78-0012. Appendix 1-0013, Appendix 2-004.

_____. *Disclosure of Research Information Under the Freedom of Information Act*. Washington, DC: US Government Printing Office, 1977. DHEW # (OS) 77-0003.

_____. *Report and Recommendations: Ethical Guidelines for the Delivery of Health Services for DHEW*. Washington, DC: US Government Printing Office, 1978. DHEW # (OS) 78-0011.

_____. *Report and Recommendations: Institutional Review Boards*. Washington, DC: US Government Printing Office, 1978. DHEW # (OS) 78-0008, Appendix -0009.

_____. *Report and Recommendations: Research Involving Children*. Washington, DC: US Government Printing Office, 1977. DHEW # (OS) 77-0004.

_____. *Report and Recommendations: Research Involving Prisoners*. Washington, DC: US Government Printing Office, 1976. DHEW # (OS) 76-131.

_____. *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm*. Washington, DC: US Government Printing Office, 1978. DHEW # (OS) 78-0006, Appendix -0007.

_____. *Report and Recommendations: Research on the Fetus*. Washington, DC: US Government Printing Office, 1975. DHEW # (OS) 76-127, Appendix -128.

_____. *Report and Recommendations: Psychosurgery*. Washington, DC: US Government Printing Office, 1977. DHEW # (OS) 77-0001.

_____. *Special Study: Implications of Advances in Biomedical and Behavioral Research*. Washington, DC: US Government Printing Office, 1978. DHEW # (OS) 78-0015.

President's Commission

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Compensating for Research Injuries*. Washington, DC: US Government Printing Office, 1982.

_____. *Implementing Human Research Regulations*. Washington, DC: US Government Printing Office, 1983.

_____. *Protecting Human Subjects: First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies and Their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research*. Washington, DC: US Government Printing Office.

Ethics Advisory Committee

Ethics Advisory Board. "Report and Conclusions: HEW Support of Research Involving Human *In Vitro* Fertilization and Embryo Transfer." Washington, DC: Dept. of Health, Education and Welfare, 4 May 1979.

US Regulations

"Protection of human subjects: policies and procedures." Federal Register 38: 31738-49, 1973.

"Protection of human subjects: Federal Register 39: 18914-20, 1974.

"Protection of human subjects: technical amendments." Federal Register 40: 11854-8, 1975.

"Protection of human subjects: fetuses, pregnant women and in vitro fertilization." Federal Register 40: 33536-51, 1975.

"Protection of human subjects: research involving prisoners." Federal Register 42: 3076-91, 1977.

"Ethical principles in the conduct of research with human participants." Committee for the Protection of Human Participants in Research, American Psychological Association, Inc., August 1982.

"Protection of Human Subjects: Informed Consent; Standards for Institutional Review Boards for Clinical Investigations; and Clinical Investigations which may be reviewed through expedited review procedure." Federal Register 46: 8942-8980, 27 January 1981.

"Public Health Service Human Research Subjects." Federal Register 46: 8366-8392, 26 January 1981.

"Protection of Human Subjects." Code of Federal Regulations 45 CFR 46, Office of Protection from Research Risks Reports, March 8, 1983.



Selected Information Sources



1. Selected Reference Works

Goldstein Doris. *Bioethics: A Guide to Information Sources*. Detroit: Gale Research Co., 1982.

The Hastings Center's Bibliography of Ethics, Biomedicine and Professional Responsibility, published by University Publications of America, Frederick, MD, in association with the Hastings Center, 255 Elm Road, Briarcliff Manor, NY 10510, USA, 1983.

Nevins, Madeline M., ed. *Annotated Bibliography of Bioethics: Selected 1976 Titles*, Rockville, MD: Information Planning Associates, 1977.

Reich, Warren T., ed. *Encyclopedia of Bioethics*, 4 volumes. New York: Free Press, 1978.

Walters, LeRoy, ed. *Bibliography of Bioethics*, volumes 1-10. Volumes 1-6 published by Gale Research Co., volumes 7-9 published by Free Press, New York. Volume 10- published by Georgetown University (Washington, DC 20057), Joseph and Rose Kennedy Institute of Ethics.

Periodicals

Hastings Center Report (six times yearly) and *IRB: A Review of Human Subjects Research* (six times yearly). Both are published by the Hastings Center, 255 Elm Road, Briarcliff Manor, NY 10510.

2. On-line information facilities for computer searches.

Bioethicsline

Provides references to print and nonprint materials on value questions arising in biomedical and behavioral fields. Includes citations appearing in the *Bibliography of Bioethics*. Prepared by the library staff at the National Reference Center for Bioethics Literature, Kennedy Institute of Ethics for the National Library of Medicine, US, 1974 to present. About 15,000 references. MEDLARS.

Biosis (Previews)

Includes contents of Biological Abstracts and Biological Abstracts/RRM (Reports, Reviews, Meetings) covering entire life sciences field. Prepared by Bibliographic Retrieval Services (BRS). 1970 to present. Over 2 million records. BRS and Dialog Information Services, Inc. (DIALOG). Also CAN/OLE.

Mediine

Worldwide professional literature in the biomedical sciences. Same data base as the printed Index Medicus. Current journals of recent years. Prepared by National Library of Medicine, US, and available in Canada through CISTI-sponsored MEDLINE centres (Canada Institute for Scientific and Technical Information, National Research Council, Ottawa K1A 0S2.) BRS, DIALOG and MEDLARS.

Mental Health Abstracts

Covers international mental health literature selected from approximately 950 journals, symposia, government reports, etc. Prepared by the National Institutes of Mental Health. 1969 to present. Over 400,000 records. DIALOG.

Public Affairs Information Service International (PAIS)

International coverage of public affairs and contemporary social science literature from 1400 periodicals, books, pamphlets, and federal, state and local government documents. Includes Foreign Language Index and PAIS Bulletin. 1976 to present. Over 124,000 records. Prepared by the Public Affairs Information Service. BRS and DIALOG.

Psycinfo

Worldwide coverage of psychology and related behavioral sciences. Book reviews from Contemporary Psychology included since 1980. Printed version is Psychological Abstracts. Prepared by the American Psychological Association. 1967 to present. Over 330,000 records. BRS and DIALOG.

Scisearch (SCI)

Multidisciplinary index to the literature of science and technology, including medicine. Contains all the records published in Science Citation Index. Can be searched by author's cited references. Prepared by Institute for Scientific Information. Philadelphia: 1974 to present. About 32 million records. DIALOG. Also CAN/STI.

Social Scisearch (SSCI)

Covers sociology and related social science areas contained in the Social Sciences Citation Index. Can be searched by author's cited references. Prepared by the Institute for

Scientific Information. 1972 to present. About 2 million records. BRS and DIALOG. Also CAN/STI.

Sociological Abstracts

Covers worldwide literature in sociology and related social science disciplines. Over 1200 serials in 32 languages from 40 countries. Prepared by Sociological Abstracts, Inc. 1963 to present. Over 112,000 records. BRS and DIALOG.

3. Some Canadian Institutions involved in Bioethics.

Calgary Humanities Institute, University of Calgary, 2500 University Drive, Calgary, Alberta T2N 1N4.

Canadian Register of Research and Researchers in the Social Sciences, Sub-Register for Biomedical Ethics. University of Western Ontario, Faculty of Social Science, Social Science Computing Laboratory, London, Ontario N6A 5C2.

Canadian Student Pugwash National Office, suite 902, 151 Slater Street, Ottawa, Ontario K1P 5H3.

Center for Bioethics, Clinical Research Institute of Montreal, 110 ouest, avenue des Pins, Montreal, Quebec H2W 1R7.

Centre for Professional and Applied Ethics, University College, 500 Dysart Road, Winnipeg, Manitoba R3T 2M8.

Westminster Institute for Ethics and Human Values, Westminster College, London, Ontario N6G 2M2

University of Alberta, Joint Faculties Bioethics Project, 114 Street and University Avenue, Edmonton, Alberta T6G 2J3